EXHIBIT D

Handbook of PHARMACEUTICAL EXCIPIENTS

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Polymethacrylates

1. Nonproprietary Names

USPNF: Ammonio methacrylate copolymer
USPNF: Methacrylic acid copolymer
Note that two separate monographs applicable to polymethacrylates are contained in the USPNF, *see* Section 9.

2. Synonyms

Eudragit; polymeric methacrylates.

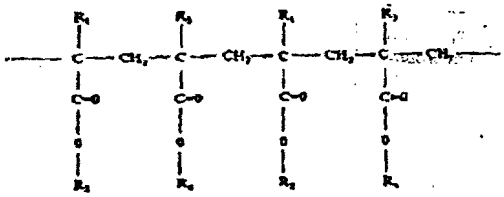
3. Chemical Name and CAS Registry Number

See Table I.

4. Empirical Formula Molecular Weight

The USPNF XVII describes methacrylic acid copolymer as a fully polymerized copolymer of methacrylic acid and an acrylic or methacrylic ester. Three types, type A (*Eudragit L*), type B (*Eudragit S*), and type C (*Eudragit L 30 D-55*), are defined which vary in their methacrylic acid content and solution viscosity. Two additional polymers, type A (*Eudragit RL*) and type B (*Eudragit RS*), also referred to as ammonio methacrylate copolymers, consisting of fully polymerized copolymers of acrylic acid and methacrylic acid esters with a low content of quaternary ammonium groups, are also described in the USPNF XVII. *See* Section 9.
Typically, the molecular weight of the polymer is ≥ 100 000.

5. Structural Formula



For *Eudragit E*:
R_1, R_3 = CH_3
R_2 = $CH_2CH_2N(CH_3)_2$
R_4 = CH_3, C_4H_9
For *Eudragit L* and *S*:
R_1, R_3 = CH_3
R_2 = H
R_4 = CH_3
For *Eudragit RL* and *RS*:
R_1 = H, CH_3
R_2 = CH_3, C_2H_5
R_3 = CH_3
R_4 = $CH_2CH_2N(CH_3)_3^+Cl^-$
For *Eudragit NE 30 D*:
R_1, R_2 = H, CH_3
R_2, R_4 = CH_3, C_2H_5
For *Eudragit L 30 D-55* and *L 100-55*:
R_1, R_2 = H, CH_3
R_2 = H
R_4 = CH_3, C_2H_5

6. Functional Category

Film-former; tablet binder; tablet diluent.

7. Applications in Pharmaceutical Formulation or Technology

Polymethacrylates are primarily used in oral capsule and tabl formulations as film coating agents.[1-10] Depending on th type of polymer used, films of different solubility characte istics can be produced, *see* Table III.
Eudragit E is used as a plain or insulating film former; it soluble in gastric fluid below pH 5. In contrast, *Eudragit L* an *S* types are used as enteric coating agents since they a resistant to gastric fluid. Different types are available whic are soluble at different pH values, e.g. *Eudragit L 100* is solubl at > pH 6, *Eudragit S 100* is soluble at > pH 7.
Eudragit RL, *RS* and *NE 30 D* are used to form wate insoluble film coats for sustained release products. *Eudrag RL* films are more permeable than those of *Eudragit RS*, an by mixing the two types together films of varying permeabilit can be obtained. *Eudragit L 100-55* is a redispersible powde and is an alternative to *Eudragit L 30 D-55* for aqueous enteri coating.
Polymethacrylates are also used as binders in both aqueou and organic wet-granulation processes. Larger quantities (5 20%) of dry polymer are used to control the release of a active substance from a tablet matrix. Solid polymers may b used in direct compression processes in quantities of 10-50% Polymethacrylate polymers may additionally be used to form the matrix layers of transdermal delivery systems and have also been used to prepare novel gel formulations for recta administration.[11]
See also Section 19.

8. Description

Polymethacrylates are synthetic cationic and anionic polymers of dimethylaminoethylmethacrylates, methacrylic acid and methacrylic acid esters in varying ratios. Several differen types are commercially available and may be obtained as the dry powder, an aqueous dispersion, or as an organic solution A (60:40) mixture of acetone and propan-2-ol is mos commonly used as the organic solvent. *See* Tables I and II.
Eudragit E is cationic polymer based on dimethylaminoethy methacrylate and other neutral methacrylic acid esters. It soluble in gastric fluid as well as in weakly acidic buffe solutions (up to approximately pH 5). *Eudragit E* is availabl as a 12.5% ready-to-use solution in propan-2-ol/aceton (60:40). It is light yellow in color with the characteristic odo of the solvents. Solvent-free granules contain ≥ 98% dry weight content of *Eudragit E*.
Eudragit L and *S*, also referred to as methacrylic ac copolymers in the USPNF monograph, are anionic copol merization products of methacrylic acid and methyl meth crylate. The ratio of free carboxyl groups to the ester approximately 1:1 in *Eudragit L* and approximately 1:2 *Eudragit S*. Both polymers are readily soluble in neutral weakly alkaline conditions (pH 6-7) and form salts wi alkalis, thus affording film coats which are resistant to gastr media but soluble in intestinal fluid. They are available as 12.5% solution in propan-2-ol without plasticizer (*Eudragit 12.5* and *S 12.5*); and as a 12.5% ready-to-use solution propan-2-ol with 1.25% dibutyl phthalate as plasticiz (*Eudragit L 12.5 P* and *S 12.5 P*). Solutions are colorle with the characteristic odor of the solvent. *Eudragit L-100* a

Table I: Chemical name and CAS registry number of polymethacrylates.

Chemical name	Trade name	CAS number
Poly(butyl methacrylate, (2-dimethyl aminoethyl) methacrylate, methyl methacrylate) 1:2:1	*Eudragit E 100* *Eudragit E 12.5*	[24938-16-7]
Poly(ethyl acrylate, methyl methacrylate) 2:1	*Eudragit NE 30 D* (formerly *Eudragit 30 D*)	[9010-88-2]
Poly(methacrylic acid, methyl methacrylate) 1:1	*Eudragit L 100* *Eudragit L 12.5* *Eudragit L 12.5 P*	[25806-15-1]
Poly(methacrylic acid, ethyl acrylate) 1:1	*Eudragit L 30 D-55* *Eudragit L 100-55*	[25212-88-8]
Poly(methacrylic acid, methyl methacrylate) 1:2	*Eudragit S 100* *Eudragit S 12.5* *Eudragit S 12.5 P*	[25086-15-1]
Poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.2	*Eudragit RL 100* *Eudragit RL PO* *Eudragit RL 30 D* *Eudragit RL 12.5*	[33434-24-1]
Poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.1	*Eudragit RS 100* *Eudragit RS PO* *Eudragit RS 30 D* *Eudragit RS 12.5*	[33434-24-1]

Eudragit S-100 are white free flowing powders with at least 95% of dry polymers.

Eudragit RL and *Eudragit RS*, also referred to as ammoniomethacrylate copolymers in the USPNF monograph, are copolymers synthesized from acrylic acid and methacrylic acid esters with *Eudragit RL* (type A) having 10% of functional quaternary ammonium groups and *Eudragit RS* (type B) having 5% of functional quaternary ammonium groups. The ammonium groups are present as salts and give rise to pH-independent permeability of the polymers. Both polymers are water-insoluble, and films prepared from *Eudragit RL* are freely permeable to water, whereas, films prepared from *Eudragit RS* are only slightly permeable to water. They are available as 12.5% ready-to-use solutions in propan-2-ol/acetone (60:40). Solutions are colorless or slightly yellow in color, and may be clear or slightly turbid; they have an odor characteristic of the solvents. Solvent-free granules (*Eudragit RL 100* and *Eudragit RS 100*) contain ≥ 97% of the dried weight content of the polymer.

Eudragit RL PO and *Eudragit RS PO* are fine, white powders with a slight amine-like odor. They are characteristically the same polymers as *Eudragit RL* and *RS*. They contain ≥ 97% of dry polymer.

Eudragit RL 30 D and *Eudragit RS 30 D* are aqueous dispersions of copolymers of acrylic acid and methacrylic acid esters with a low content of quaternary ammonium groups. The dispersions contain 30% polymer. The quaternary groups occur as salts and are responsible for the permeability of films made from these polymers. Films prepared from *Eudragit RL 30 D* are readily permeable to water and to dissolved active substances, whereas films prepared from *Eudragit RS 30 D* are less permeable to water. Film coatings prepared from both polymers give pH-independant release of active substance. Plasticizers are usually added to improve film properties.

Eudragit NE 30 D is an aqueous dispersion of a neutral copolymer consisting of polymethacrylic acid esters. The dispersions are milky-white liquids of low viscosity and have a weak aromatic odor. Films prepared from the lacquer swell in water, to which they become permeable. Thus, films produced are insoluble in water, but give pH-independent drug release.

Eudragit L 30 D-55 is an aqueous dispersion of an anionic copolymer based on methacrylic acid and acrylic acid ethyl ester. The polymer corresponds to USPNF methacrylic acid copolymer, type C. The ratio of free carboxyl groups to ester groups is 1:1. Films dissolve above pH 5.5 forming salts with alkalis, thus affording coatings which are insoluble in gastric media, but soluble in the small intestine.

Eudragit L 100-55 (prepared by spray-drying *Eudragit L 30 D-55*) is a white, free-flowing powder which is redispersible in water to form a latex which has properties similar to *Eudragit L 30 D-55*.

9. Pharmacopeial Specifications

Specifications for methacrylic acid copolymers (*Eudragit L, S and L 30 D-55*).

Test	USPNF XVII (Suppl 6)
Identification	+
Viscosity	
Type A	50-200 mPa s
Type B	50-200 mPa s
Type C	100-200 mPa s
Loss on drying	
Type A	≤ 5.0%
Type B	≤ 5.0%
Type C	≤ 3.0%
Residue on ignition	
Type A	≤ 0.1%
Type B	≤ 0.1%
Type C	≤ 0.4%
Arsenic	≤ 2 ppm
Heavy metals	≤ 0.002%
Monomers	≤ 0.3%
Assay of methacrylic acid units (dried basis)	
Type A	46.0-50.6%
Type B	27.6-30.7%
Type C	46.0-50.6%

Specifications for ammonio methacrylate copolymers (*Eudragit RL* and *RS*).

Test	USPNF XVII (Suppl 4)
Identification	+
Viscosity	
Types A and B	≤ 15 mPa s
Loss on drying	
Types A and B	≤ 3.0%
Residue on ignition	
Types A and B	≤ 0.1%
Arsenic	≤ 2 ppm
Heavy metals	≤ 0.002%
Monomers	≤ 0.3%
Assay of ammonio methacrylate units (dried basis)	
Type A	8.85-11.96%
Type B	4.48-6.77%

10. Typical Properties

Acid value: 315 for *Eudragit L 12.5*, *L 12.5 P*, *L 100*, *L 30 D-55*, and *L 100-55*; 180-200 for *Eudragit S 12.5*, *S 12.5 P*, and *S 100*.

Alkali value:
162-198 for *Eudragit E 12.5* and *E 100*;
23.9-32.3 for *Eudragit RL 12.5*, *RL 100*, and *RL PO*;
27.5-31.7 for *Eudragit RL 30 D*;
12.1-18.3 for *Eudragit RS 12.5*, *RS 100*, and *RS PO*;
16.5-22.3 for *Eudragit RS 30 D*.

Density:
0.81-0.82 g/cm³ for *Eudragit E*;
0.83-0.85 g/cm³ for *Eudragit L*, *S 12.5* and *12.5 P*;
0.83-0.85 g/cm³ for *Eudragit L*, *S 100*;
1.06-1.07 g/cm³ for *Eudragit L 30 D-55*;
0.82-0.84 g/cm³ for *Eudragit L 100-55*;
0.815-0.835 g/cm³ for *Eudragit RL* and *RS 12.5*;
0.815-0.835 g/cm³ for *Eudragit RL* and *RS PO*;
1.045-1.055 g/cm³ for *Eudragit RL* and *RS 30 D*.

Refractive index:
n_D^{20} = 1.38-1.385 for *Eudragit E*;
n_D^{20} = 1.39-1.395 for *Eudragit L* and *S*;
n_D^{20} = 1.387-1.392 for *Eudragit L 100-55*;
n_D^{20} = 1.38-1.385 for *Eudragit RL* and *RS*.

Solubility: *see* Table II.

Viscosity (dynamic):
3-12 mPa s for *Eudragit E*;
50-200 mPa s for *Eudragit L* and *S*;
≤ 50 mPa s for *Eudragit L 30 D-55*;
100-200 mPa s for *Eudragit L 100-55*;
≤ 15 mPa s for *Eudragit RL* and *RS*;
≥ 200 mPa s for *Eudragit RL* and *RS D*.

Table II: Solubility of commercially available polymethacrylates (*Eudragit*, Röhm Pharma GmbH) in various solutions.

Type	Solvent: Acetone and alcohols[a]	Dichloromethane	Ethyl acetate	1N HCl	1N NaOH	Petroleum ether	Water
Eudragit E 12.5	M	M	M	M	—	M	—
Eudragit E 100	S	S	S	—	—	I	I
Eudragit L 12.5 P	M	M	M	—	M	P	P
Eudragit L 12.5	M	M	M	—	M	P	P
Eudragit L 100-55	S	I	I	—	S	I	I
Eudragit L 100	S	I	I	—	S	I	I
Eudragit L 30 D-55[b]	M[c]	—	—	—	M[c]	—	M
Eudragit S 12.5 P	M	M	M	—	M	P	P
Eudragit S 12.5	M	M	M	—	M	P	P
Eudragit S 100	S	I	I	—	S	I	I
Eudragit RL 12.5	M	M	M	—	—	P	M
Eudragit RL 100	S	S	S	—	—	I	I
Eudragit RL PO	S	S	S	—	I	I	I
Eudragit RL 30 D	M[d]	M	M	—	I	I	M
Eudragit RS 12.5	M	M	M	—	—	P	M
Eudragit RS 100	S	S	S	—	—	I	I
Eudragit RS PO	S	S	S	—	I	I	I
Eudragit RS 30 D	M[e]	M	M	—	I	I	M

Where: S = soluble;
M = miscible;
I = insoluble or immiscible;
P = precipitates.

Note: a. Alcohols including ethanol, methanol and propan-2-ol.
b. Supplied as a milky-white colored aqueous dispersion.
c. A 1:5 mixture forms a clear, viscous, solution.
d. A 1:2 mixture forms a clear or slightly opalescent, viscous liquid.
e. A 1 part of both *Eudragit RL 30 D* and *Eudragit RS 30 D* dissolve completely in 5 parts acetone, ethanol or propan-2-ol to form a clear or slightly turbid solution. However, when mixed in a ratio of 1:5 with methanol, *Eudragit RL 30 D* dissolves completely, whereas *Eudragit RS 30 D* only partially.

11. Stability and Storage Conditions

Dry powder polymer forms are stable at temperatures less than 30°C. Above this temperature, powders tend to form clumps although this does not affect the quality of the substance and the clumps can be readily broken up. Dry powders are stable for at least two years if stored in a tightly closed container at less than 30°C.

Dispersions are sensitive to extreme temperatures and phase separation occurs below 0°C. Dispersions should therefore be stored at temperatures between 5-25°C and are stable for at least one year after shipping from the manufacturer's warehouse if stored in a tightly closed container at the above conditions.

12. Incompatibilities

Incompatibilities occur with certain polymethacrylate dispersions depending upon the ionic and physical properties of the polymer and solvent. For example, coagulation may be caused by soluble electrolytes, pH changes, some organic solvents and extremes of temperature, *see* Table II. Dispersions of *Eudragit L 30 D*, *RL 30 D*, *L 100-55* and *RS 30 D* are also incompa with magnesium stearate.

Interactions between polymethacrylates and some drugs occur although solid polymethacrylates and organic soluti are generally more compatible than aqueous dispersions.

13. Method of Manufacture

Prepared by the polymerization of acrylic and methacr acids or their esters, e.g. butyl ester or dimethylaminoet ester.

14. Safety

Polymethacrylate copolymers are widely used as film coati materials in oral pharmaceutical formulations. They are al used to a lesser extent in topical formulations and are genera regarded as nontoxic and nonirritant materials.

A daily intake of 2 mg/kg body-weight of *Eudragit* (equivale to approximately 150 mg for an average adult) may l regarded as essentially safe in humans.

See also Section 15.

Table III: Summary of properties and uses of commercially available polymethacrylates (*Eudragit*, Röhm Pharma GmbH).

Type	Supply form	Polymer dry weight content	Recommended solvents or diluents	Solubility	Applications
Eudragit E 12.5	Organic solution	12.5%	Acetone, alcohols	Soluble in gastric fluid to pH 5	Film coating
Eudragit E 100	Granules	98%	Acetone, alcohols	Soluble in gastric fluid to pH 5	Film coating
Eudragit L 12.5 P	Organic solution	12.5%	Acetone, alcohols	Soluble in intestinal fluid from pH 6	Enteric coatings
Eudragit L 12.5	Organic solution	12.5%	Acetone, alcohols	Soluble in intestinal fluid from pH 6	Enteric coatings
Eudragit L 100	Powder	95%	Acetone, alcohols	Soluble in intestinal fluid from pH 6	Enteric coatings
Eudragit L 100-55	Powder	95%	Acetone, alcohols	Soluble in intestinal fluid from pH 5.5	Enteric coatings
Eudragit L 30 D-55	Aqueous dispersion	30%	Water	Soluble in intestinal fluid from pH 5.5	Enteric coatings
Eudragit S 12.5 P	Organic solution	12.5%	Acetone, alcohols	Soluble in intestinal fluid from pH 7	Enteric coatings
Eudragit S 12.5	Organic solution	12.5%	Acetone, alcohols	Soluble in intestinal fluid from pH 7	Enteric coatings
Eudragit S 100	Powder fluid	95%	Acetone, alcohols	Soluble in intestinal from pH 7	Enteric coatings
Eudragit RL 12.5	Organic solution	12.5%	Acetone, alcohols	High permeability	Sustained release
Eudragit RL 100	Granules	97%	Acetone, alcohols	High permeability	Sustained release
Eudragit RL PO	Powder	97%	Acetone, alcohols	High permeability	Sustained release
Eudragit RL 30 D	Aqueous dispersion	30%	Water	High permeability	Sustained release
Eudragit RS 12.5	Organic solution	12.5%	Acetone, alcohols	Low permeability	Sustained release
Eudragit RS 100	Granules	97%	Acetone, alcohols	Low permeability	Sustained release
Eudragit RS PO	Powder	97%	Acetone, alcohols	Low permeability	Sustained release
Eudragit RS 30 D	Aqueous dispersion	30%	Water	Low permeability	Sustained release
Eudragit NE 30 D	Aqueous dispersion	30% or 40%	Water	Swellable, permeable	Sustained release, tablet matrix

Note: Recommended plasticizers for the above types of *Eudragit* polymers include dibutyl phthalate, polyethylene glycols and triethyl citrate. Approximately 20% plasticizer is required for *Eudragit RL 30 D* and *Eudragit RS 30 D*. A plasticizer is not necessary with *Eudragit E 12.5*, *Eudragit E 100* and *Eudragit NE 30 D*.

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Additional measures should be taken when handling organic solutions of polymethacrylates. Eye protection, gloves and a dust mask or respirator are recommended. Polymethacrylates should be handled in a well-ventilated environment and measures taken to prevent dust formation.

Acute and chronic adverse effects have been observed in workers handling the related substances methyl methacrylate and poly(methyl methacrylate) (PMMA).[12,13] In the UK, the occupational exposure limit for methyl methacrylate has been set at 410 mg/m^3 (100 ppm) long-term (8-hour TWA), and 510 mg/m^3 (125 ppm) short-term.[14]

See also Section 18.

16. Regulatory Status

Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK.

17. Pharmacopeias

Fr and USPNF.

18. Related Substances

Methyl methacrylate; poly(methyl methacrylate).

Methyl methacrylate: $C_5H_8O_2$
Molecular weight: 100.13
CAS number: [80-62-6]
Synonyms: methacrylic acid, methyl ester; methyl 2-methacrylate; methyl 2-methylpropenoate; MME.
Comments: methyl methacrylate forms the basis of acrylic bone cements used in orthopaedic surgery.

Poly(methyl methacrylate): $(C_5H_8O_2)_n$
Synonyms: methyl methacrylate polymer; PMMA.
Comments: poly(methyl methacrylate) has been used as a material for intra-ocular lenses, for denture bases and as a cement for dental prostheses.

19. Comments

A number of different polymethacrylates are commercially available which have different applications and properties, *see* Table III.

For spray-coating, polymer solutions and dispersions should be diluted with suitable solvents. Some products need the addition of a plasticizer such as: dibutyl sebacate; dibutyl phthalate; glyceryl triacetate and polyethylene glycol. Different types of plasticizer may be mixed to optimize the polymer properties for special requirements.

20. Specific References

1. Lehmann K, Dreher D. The use of aqueous synthetic-polymer dispersions for coating pharmaceutical dosage forms. Drugs Made Ger 1973; 16: 126, 131, 132, 134, 136.
2. Lehmann K. Acrylic coatings in controlled release tablet manufacture I. Mfg Chem Aerosol News 1973; 44(5): 36-38.
3. Lehmann K. Acrylic coatings in controlled release tablet manufacture II. Mfg Chem Aerosol News 1973; 44(6): 39-41.
4. Lehmann K. Polymer coating of tablets - a versatile technique. Mfg Chem Aerosol News 1974; 45(5): 48, 50.
5. Gurny R, Guitard P, Buri P, Sucker H. Realization and rheoretical development of controlled-release drug forms using methacrylate films 3: preparation and characterization of controlled-release drug forms [in French]. Pharm Acta Helv 1977; 52: 182-187.
6. Lehmann K, Dreher D. Coating of tablets and small particles with acrylic resins by fluid bed technology. Int J Pharm Technol Prod Manuf 1983; 2(4): 31-43.
7. Dew MJ, Hughes PJ, Lee MG, Evans BK, Rhodes J. An oral preparation to release drugs in the human colon. Br J Clin Pharmacol 1982; 14: 405-408.
8. Lehmann K. Formulation of controlled release tablets with acrylic resins. Acta Pharm Penn 1984; 93: 55-74.
9. Lehmann K. Acrylic latices from redispersible powders for peroral and transdermal drug formulations. Drug Dev Ind Pharm 1986; 12: 265-287.
10. Lehmann K, Dreher D. Mixtures of aqueous polymethacrylate dispersions for drug coating. Drugs Made Ger 1988; 31: 101-102.
11. Umejima H, Kiso N-S, Ito T, Uchida T, Goto S. Preparation and evaluation of Eudragit gels VI: in vivo evaluation of Eudispert rectal hydrogel and Xerogel containing salicylamide. J Pharm Sci 1993; 82: 195-199.
12. Routledge R. Possible hazard of contact lens manufacture [letter]. Br Med J 1973; 1: 487-488.
13. Burchman S, Wheater RH. Hazard of methyl methacrylate to operating room personnel. JAMA 1976; 235: 2652.
14. Health and Safety Executive. EH40/93: occupational exposure limits, 1993. London: HMSO, 1993.

21. General References

McGinity JW. Aqueous polymeric coatings for pharmaceutical dosage forms. New York: Marcel Dekker Inc, 1989.

Röhm Pharma GmbH. Technical literature: *Eudragit*, 1990.

22. Authors

USA: AJ Shukla.